Liver transplantation after paracetamol overdose

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Abstract

Objective—To evaluate the role of liver transplantation after paracetamol overdose.

Design—Prospective study of consecutive candidates for transplantation and performance of transplantation over 18 months.

Setting—Liver unit, King's College Hospital, London.

Main outcome measures—Fulfilment of indicators of poor prognosis, selection for transplantation, transplantation, survival.

Results—30 of 37 patients considered to have a reasonable prognosis with intensive medical care survived. Of 14 of 29 patients considered to have a very poor prognosis and registered for urgent liver transplantation, six received liver transplants, four of whom survived, while seven died and one survived without a transplant. Three of 15 patients with poor prognostic indicators but not selected for transplantation survived.

Conclusion—Liver transplantation will have a definite but limited role in the management of fulminant hepatic failure induced by paracetamol.

Introduction

Paracetamol overdose remains the commonest cause of fulminant hepatic failure in the United Kingdom, causing at least 100 deaths a year and accounting for over half of the cases admitted to the liver failure unit at King's College Hospital.^{1,2} Despite considerable advances in the medical management of these patients about half of those progressing to grade IV encephalopathy die.³ A recent study from this unit, based on an analysis of 431 patients, showed that over three quarters of fatal cases could be identified with two criteria based on clinical and laboratory findings—an arterial pH <7.30 on the second or subsequent day after the overdose or, at a later stage, the coexistence of a prothrombin time >100 s, serum creatinine concentration >300 µmol/l, and grade III or IV encephalopathy.⁴ In contrast, 89% of patients not meeting these criteria survived.

The unexpected, but now well documented, success of orthotopic liver transplantation in acute liver failure⁵⁻⁹ has led to it being considered for treating paracetamol overdose. Although the self inflicted nature of the injury might be taken as a contraindication to liver transplantation,¹⁰ we believe that most of these patients have excellent long term psychiatric prognoses and should therefore be accorded the full range of available treatments. The prognostic criteria described above should accurately identify patients who on medical grounds would merit a liver transplant. Although there have been anecdotal references to liver transplantation for paracetamol induced fulminant hepatic failure,^{6,11} this report is the first systematic assessment of its role.

Patients and methods

We decided to consider patients who develop fulminant hepatic failure after a paracetamol overdose

for orthotopic liver transplantation in October 1988, after the prognostic criteria had been formulated. Between October 1988 and 31 March 1990, 66 patients were admitted to the liver failure unit because of severe liver damage after a paracetamol overdose. The patients were assessed both medically and psychiatrically and classified into three subgroups: 37 patients with a reasonable chance of survival with supportive medical care; 15 patients with a poor prognosis who, for various reasons detailed below, were not registered for liver transplantation; and 14 patients with a poor prognosis in whom a decision to transplant was made and who were subsequently placed on the "super urgent" waiting list for a donor organ with the United Kingdom Transplant Service. Of the 29 patients in the latter groups, 20 were identified by the presence of an arterial pH <7.30 (10 in each group) and nine patients (six in the second group and three in the third group) by the concomitant presence of a prothrombin time >100 s, serum creatinine concentration >300 µmol/l, and encephalopathy of at least grade III severity.

Contraindications to transplantation, either on admission or later during the hospital stay, included the presence of active sepsis (pneumonia or positive culture not treated with appropriate antibiotics for 48 hours), refractory systemic hypotension (manifested by a systolic pressure <90 mm Hg despite inotropic support), and evidence of impaired brain stem function as a consequence of cerebral oedema. Renal failure or cerebral oedema that was controlled by medical management (mannitol with or without ultrafiltration or sodium thiopentone as appropriate) was not considered to be a contraindication. All patients received full appropriate intensive care as detailed elsewhere.¹¹

The psychiatric contraindications were a history of repeated suicide attempts or a desire to die stated persistently before the onset of clinical encephalopathy. Whenever possible the potential candidates for transplantation were assessed by the duty psychiatrist if encephalopathy had not yet developed, and the patient's attitude to possible liver transplantation was probed. The decision to proceed was always discussed with the immediate family.

Results

Thirty of the 37 patients in the group given supportive medical care survived (fig 1); six of the deaths were due to cerebral oedema and the seventh to sepsis after recovery from encephalopathy.

Ten of the 15 patients with criteria indicating a poor prognosis but who were not registered for transplantation were excluded by the presence of other medical findings (four with refractory hypotension, four with active sepsis, two with severe cerebral oedema). Three others were excluded on psychiatric grounds: one was a severe alcoholic, one had a long history of suicide attempts, and one clearly indicated her lack of regret about the overdose and reiterated her desire to die. The remaining two patients had no specific contraindications at the time of admission, but it was not possible to proceed to transplantation for logistical reasons—

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FIG 1—Outcome in 66 patients admitted after paracetamol overdose

that is, prior commitment of resources to elective operations. The median peak prothrombin time for the 15 patients in this group was 120 (range 80 to >180) s and the median peak serum creatinine concentration was 310 (100-600) $\mu\text{mol/l}$. Progression of encephalopathy was observed to grade III in two patients and to grade IV in the 13 others, 10 of whom showed clinical signs of cerebral oedema. Only three patients survived. Seven of the deaths occurred within 48 hours of admission from hypotension or cerebral oedema; the other five patients survived for 6-16 days before succumbing to sepsis.

The 14 patients suitable for liver transplantation were registered within 24 hours of admission. The values for median peak prothrombin time of >180 s (lowest 110 s) and median peak serum creatinine concentration of 410 (315-665) $\mu\text{mol/l}$ were broadly similar to those seen in the 15 patients not registered for transplantation. Donor organs compatible for ABO blood group were found for seven patients within two to seven days of admission, and six of these received transplants (table). The reversal of encephalopathy was rapid in each instance and the patients were extubated 48-72 hours after operation. Four of the six patients survived, three of whom required haemodialysis for continued renal failure for three weeks, while the fourth started to pass urine 36 hours after transplantation and needed dialysis for only a short time. The two deaths occurred at 10 days and 10 weeks despite satisfactory liver function, as a consequence of hepatic artery erosion by *Aspergillus fumigatus* in one case and chronic sepsis with respiratory failure in the other.

The seventh patient for whom a donor organ was found was withdrawn from transplantation. She had been admitted 48 hours after the overdose, and on the basis of a previously documented arterial pH of 7.05 at the referring hospital she was registered for transplantation (arterial pH on admission 7.38). On the

third day after the overdose she also fulfilled the alternative selection criteria, having a prothrombin time of 165 s, serum creatinine concentration of 381 $\mu\text{mol/l}$, and grade III encephalopathy. She developed grade IV encephalopathy without evidence of cerebral oedema and required mechanical ventilation, haemodialysis, inotropic support, and antibiotics. A suitable graft did not become available until the eighth day after the overdose, but by then prothrombin time had fallen to 48 s and the encephalopathy had lightened to grade II. Consequently it was decided to persist with medical management and the patient was withdrawn from transplantation. This patient survived to leave hospital five weeks after admission.

The remaining seven patients not receiving transplants developed medical contraindications to transplantation (four developed sepsis, two hypotension, and one cerebral oedema) before donor livers became available, and all subsequently died. Thus only four of the 23 patients who had been assessed as needing a liver transplant but who did not receive it survived. The time between the overdose and admission to the liver failure unit, development of medical contraindications to transplantation, and death was studied in this cohort (fig 2). Referral of these patients had been prompt, with all but one being admitted by the end of the third day after the overdose. Over half of the patients developed medical contraindications to transplantation by the end of day 5 (range days 2-11), giving a median "window period" when transplantation was feasible of only two days after admission. Examination of the distribution of the intervals between the overdose and transplantation in the six patients who received transplants showed that these corresponded closely with this window period.

LONG TERM FOLLOW UP OF PATIENTS RECEIVING TRANSPLANTS

The four patients who survived transplantation were followed for 14-30 months. Three were fully rehabilitated: results of liver function tests were normal. The fourth had perfect liver function when seen 49 weeks after transplantation but presented again five weeks later with intractable rejection, apparently precipitated by an episode of poor compliance with immunosuppressive treatment. The patient was not cooperative, to the extent of leaving hospital against medical advice, and the outcome at the time of writing was uncertain. Renal function was normal in all four patients, and standard maintenance immunosuppression with cyclosporin in addition to prednisolone and azathioprine was used.

Before the episode described above rehabilitation had been excellent in each patient. No further suicide attempts were known. The three patients who remained well had taken the overdose because of marital difficulties. Two separated from their spouses and one overcame the problems within the existing relationship. Three of the four were in full time employment and the fourth was a homemaker.

Discussion

These data show that in a group of patients with severe liver damage 43% could be identified as having a very poor prognosis. Although patients were referred promptly, about half had already developed medical complications (refractory hypotension, severe cerebral oedema, active sepsis) which were likely greatly to decrease the chances of successful transplantation. Half of the remainder developed similar medical complications before a suitable donor organ could be obtained. We considered these complications to be contraindications to transplantation. This suggests that liver transplantation will play a definite but limited

Clinical characteristics of patients treated by liver transplantation after paracetamol overdose

	Case No					
	1	2	3	4	5	6
Sex	M	F	M	F	F	F
Age (years)	35	40	27	42	28	27
Criteria at time of admission:						
Arterial pH	7.13	Not done	7.48	7.38	7.34	7.15
Peak prothrombin time (s)	>180	>180	>180	150	170	>150
Creatinine ($\mu\text{mol/l}$)	665	365	395	576	323	462
Encephalopathy (grade)	IV	IV	IV	IV	IV	IV
Cerebral oedema	No	No	Yes	Yes	No	Yes
Days from overdose to admission	2	2	2	2	1.5	3
Days from overdose to transplantation	6	4	5	9	4	4
Outcome	Alive	Alive	Alive	Dead	Dead	Alive

FIG 2—Time between paracetamol overdose and admission to liver failure unit, development of medical contraindications to transplantation, and death for 23 patients with indicators of a poor prognosis but not treated by liver transplantation

part in the management of fulminant hepatic failure induced by paracetamol.

The median interval between admission and both the development of medical contraindications and successful transplantation was only two days. A number of strategies might be adopted to attempt to widen this window period. Although prompt referral of suitable patients is essential, our experience suggests that there is only modest scope for improvement in this. Wider recognition of the prognostic importance of a metabolic acidosis, as defined above, might lead to more referrals on the second day after the overdose. This indicator was present in 69% of those considered to have a poor prognosis in this study. Unfortunately, in the remaining patients fairly accurate prognostication was delayed, thus reducing the time available for intervention with transplantation. Some recent evidence suggests that a continued rise in prothrombin time from day 3 to day 4 after drug ingestion is associated with a poor prognosis.¹³ This criterion was not used in the present study, but it may permit earlier identification of fatal cases than the combination of a prothrombin time >100 s (international normalised ratio approximately 6.7), serum creatinine concentration >300 µmol/l, and encephalopathy of at least grade III severity in the patients not having a metabolic acidosis. This combination, together with a metabolic acidosis, was a reasonably good indicator as far as overall survival was concerned, with only 17% of these cases recovering as compared with 81% in the group without these indicators.

A second approach to widening the window period is more effective control of, and support for, the consequences of fulminant hepatic failure. The management of these patients, either with or without liver transplantation, requires complex intensive medical care, but new measures of three variables—cerebral oedema, sepsis, and haemodynamic instability—could increase the time during which patients are fit for transplantation. Some recent evidence suggests that giving acetylcysteine later than the currently recommended time after the overdose may be beneficial and may even improve survival.¹

An assessment of psychiatric state and prognosis is difficult in people with fulminant hepatic failure. It has been well established, however, that many people who take paracetamol overdoses are parasuicidal, especially when overdosing is an impulsive gesture in adolescents and young adults. An expression of regret, and of a desire to survive, can often be obtained when the patient is first admitted to hospital and before the onset of encephalopathy. In patients who are encephalopathic on presentation (thus rendering psychiatric assessment incomplete) and whose overdose was

precipitated by a major life crisis such as breakup of their marriage or long term relationship, pregnancy, or bereavement the psychiatric prognosis can also be excellent. Nevertheless, there can be a major problem in assessing individual cases. This was highlighted by one of our patients, who declined liver transplantation before he became encephalopathic after an overdose precipitated by the death of his mother. The psychiatric assessment led to a diagnosis of a severe grief reaction, which was considered to have an excellent prognosis with appropriate psychiatric intervention should medical recovery be attainable, an outcome considered possible only with transplantation. The patient refused this option. The advice of a medical defence body was sought, and the view held was that this was a "no win" situation. In this instance the dilemma was eased by the death of the patient before a suitable donor liver was offered.

The results of liver transplantation in acute liver failure are improving and current one year survival rates range from 55% to 80%.⁴⁹ Although the numbers are small, four out of six survivors in those receiving transplants is a rate similar to the results in groups with other causes of liver failure. Awareness of this possible management option should lead to early referral of suitable patients to units offering the combined services of liver transplantation and full supportive medical treatment. It was somewhat disappointing that we were able to find donor organs for only half of these patients over the short time that transplantation was possible, despite using the United Kingdom Transplant Service's super urgent status, which gives national priority to these patients. Hopefully, the combined effect of attempts to increase the yield of livers from the current pool of donors and the European initiative for sharing organs in super urgent cases will help alleviate this problem.

We acknowledge the many nursing, technical, and medical staff who took part in the management of these patients.

ADDENDUM

The patient whose outcome was uncertain at the time of writing died as a consequence of liver failure secondary to intractable rejection. She took a further paracetamol overdose during her terminal illness but this was not considered to have been the cause of death.

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